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CLINICAL RESEARCH
Arrhythmias

Outcomes of patients with atrial fibrillation and ischemic stroke while on oral anticoagulation

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Abstract

Aims The prognosis of patients with atrial fibrillation (AF) and ischemic stroke while taking oral anticoagulation is poorly understood. This study aimed to characterize the outcomes of patients following a stroke event while on oral anticoagulation.

Methods and results Individual participant data from five pivotal randomized trials of antithrombotic therapy in AF were used to assess the outcomes of patients with a post-randomization ischemic stroke while on study medication (warfarin, standard-, or lower-dose direct oral anticoagulant regimen) during trial follow-up. The primary outcome was recurrent ischemic stroke after the first post-randomization ischemic stroke. The primary analysis included 1163 patients with a first post-randomization ischemic stroke while on study medication (median age 73 years, 39.3% female, 35.4% history of stroke before trial enrollment). During a median continued follow-up of 337 days, 74 patients had a recurrent ischemic stroke [cumulative incidence at 1 year: 7.0%, 95% confidence interval (CI) 5.2%–8.7%]. The cumulative incidence of mortality at 3 months after stroke was 12.4% (95% CI 10.5%–14.4%). Consistent results for the incidence of recurrent ischemic stroke at 1 year were obtained in an analysis accounting for the competing risk of death (6.2%, 95% CI 4.8%–7.9%) and in a landmark analysis excluding the first 2 weeks after the index stroke and only including patients without permanent study drug discontinuation since then (6.8%, 95% CI 4.6%–8.9%).

Conclusion Patients with AF and ischemic stroke while on oral anticoagulation are at increased risk of recurrent ischemic stroke and death. These patients currently have an unmet medical need.

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Structured Graphical Abstract

Key Question

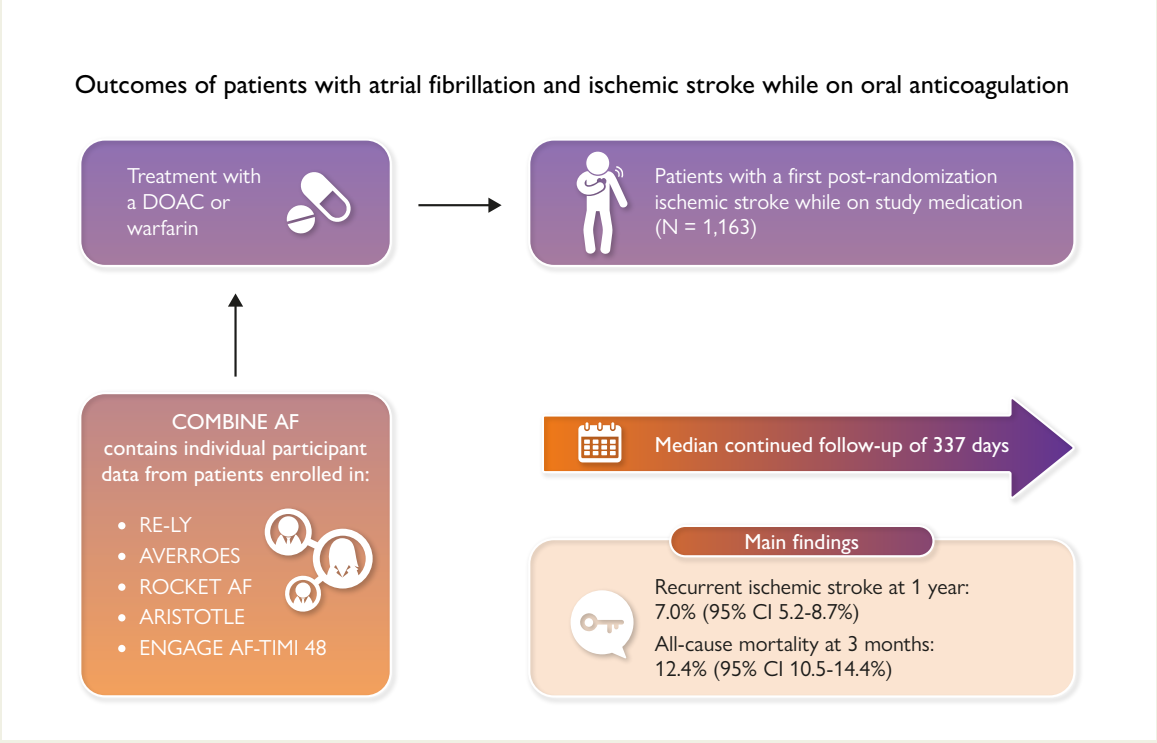
What is the risk of recurrent ischemic stroke and other outcomes in patients with atrial fibrillation who suffer an ischemic stroke while on warfarin or a direct oral anticoagulant?

Key Finding

In this COMBINE AF analysis of five randomized trials, the risk of ischemic stroke after a first post randomization stroke was 7.0% at 1 year. The risk of all-cause mortality at 3 months was 12.4%.

Take Home Message

Patients with atrial fibrillation and ischemic stroke while on oral anticoagulation are at increased risk of recurrent ischemic stroke and death. These patients currently have an unmet medical need.



Outcomes of patients with atrial fibrillation and ischemic stroke while on oral anticoagulation. Abbreviations: ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation, AVERROES, Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment, CI, confidence interval, COMBINE AF, A Collaboration Between Multiple Institutions to Better Investigate Non-Vitamin K Antagonist Oral Anticoagulant Use in Atrial Fibrillation, DOAC, direct oral anticoagulant, ENGAGE AF-TIMI 48, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48, RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy, ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

Keywords Ischemic stroke • Recurrence • Atrial fibrillation • Oral anticoagulation • DOAC • Warfarin

Introduction

Long-term oral anticoagulation with a vitamin K antagonist or a direct oral anticoagulant (DOAC) effectively reduces the risk of ischemic stroke in patients with atrial fibrillation (AF).[1,2] However, there still are patients who experience an ischemic stroke despite treatment with oral anticoagulation. The prognosis of these patients is poorly understood.

Prior cerebral ischemia is a strong risk factor for another stroke.[1] In the pivotal randomized trials of DOAC therapy in AF, rates of ischemic stroke during follow-up were increased about two-fold in patients with vs. those without prior stroke, irrespective of whether patients had been randomized to warfarin or a DOAC.[3–7] Each of these trials enrolled a subset of patients with stroke or transient ischemic attack (TIA) prior to study entry, but those with very recent stroke[8–12] and, in two of the trials, severe stroke within 3–6 months prior to enrollment were excluded.[8,10] Patients with a stroke event during trial follow-up might form a particularly high-risk subset of AF patients, but none of the individual trials was designed or sufficiently powered to assess the risk of recurrent ischemic stroke and other outcomes following a first post-randomization ischemic stroke while on study medication.

Using individual participant data from the five pivotal randomized trials of DOAC therapy in AF, merged and harmonized in the A

Collaboration Between Multiple Institutions to Better Investigate Non-Vitamin K Antagonist Oral Anticoagulant Use in AF (COMBINE AF) dataset, we aimed to estimate the incidence of recurrent ischemic stroke and mortality following a first post-randomization ischemic stroke while on warfarin or a DOAC.

Methods

Patient population

This analysis is based on individual participant data from COMBINE AF, a dataset including the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY), Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES), Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE), and Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trials of DOAC therapy in patients with AF.[8–12] Details and baseline characteristics of patients included in COMBINE AF have been published elsewhere.[13] Patients randomized to aspirin in AVERROES were excluded.[9] This analysis included all patients randomized to receive an oral anticoagulant, i.e. warfarin or a DOAC (dabigatran, apixaban, rivaroxaban, or edoxaban) who had a first post-randomization ischemic stroke before the individual censoring date for efficacy outcomes in each trial. Patients with permanent discontinuation of study drug prior to the index event were excluded. All remaining patients were assumed to have been on study medication at the time of stroke. Index stroke events that were hemorrhagic or uncertain in origin (unspecified) were not included.

Antithrombotic therapy

Patients were categorized according to randomized treatment (intention-to-treat). The first group comprised patients randomized to dose-adjusted warfarin therapy.[8,10–12] The second group comprised patients randomized to a standard-dose DOAC regimen, i.e. dabigatran, 150 mg twice daily in RE-LY,[8] apixaban 5 mg (2.5 mg if dose reduction criteria were met) twice daily in AVERROES and in ARISTOTLE,[9,11] rivaroxaban 20 mg (15 mg if dose reduction criteria were met) once daily in ROCKET AF,[10] and edoxaban 60 mg (30 mg if dose reduction criteria were met) once daily in ENGAGE AF-TIMI 48.[12] The third group consisted of patients randomized to a lower-dose DOAC regimen, i.e. dabigatran 110 mg twice daily in RE-LY[8] and edoxaban 30 mg (15 mg if dose reduction criteria were met) once daily in ENGAGE AF-TIMI 48.[12]

Outcomes

Outcome definitions were similar across trials. The primary outcome was recurrent ischemic stroke after the first post-randomization ischemic stroke, using the original trial definitions (see Supplementary data online, *Table S1*).[8–12] In the individual trials, there was central adjudication of all primary outcome events, using brain imaging by means of computed tomography and/or magnetic resonance imaging scans when available.[14–18] Secondary outcomes included permanent discontinuation of study drug, all-cause stroke (including ischemic, hemorrhagic, or uncertain etiology), and mortality following the index stroke event. All-cause stroke events that occurred on the same day as the first post-randomization ischemic stroke were deemed to have occurred after the index stroke event and were included in the analyses. Events that occurred after the censoring date for efficacy outcomes were excluded.

Statistical analysis

Baseline characteristics at the time of enrollment (i.e. not at the time of the first post-randomization ischemic stroke) were summarized as median (25–75th percentile) for continuous variables, and as counts (percentages) for categorical variables. The Kaplan–Meier method was used to estimate the cumulative incidence of recurrent ischemic stroke, all-cause stroke, and all-cause mortality following the first post-randomization ischemic stroke. Numeric estimates with 95% confidence intervals (CIs) calculated using the normal approximation method were reported for several time points following the index event.

Three sensitivity analyses were performed for the primary outcome of recurrent ischemic stroke. The first is an analysis in the original study cohort that accounted for the competing risk of death using the Fine–Gray method.[19] The second is a landmark analysis excluding the first 2 weeks after the index event, only including patients alive, at risk (i.e. prior to censoring for efficacy outcomes in the individual trials) and without permanent discontinuation of study drug through day 14 after the index event. The third is an analysis in the original study cohort but excluding patients randomized to a lower-dose DOAC regimen.

Finally, a subgroup analysis according to history of any stroke prior to study entry was done for the primary outcome.

All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, United States).

Ethical considerations

This study conforms to the principles outlined in the Declaration of Helsinki. All patients provided written informed consent, and approval from local ethics committees had been obtained prior to initiation of the RE-LY, AVERROES, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48 trials.[8–13]

Results

Patient population

Of the 74 491 patients with AF randomized to receive oral anticoagulation (warfarin, $n = 29\,272$; standard-dose DOAC, $n = 32\,170$; and lower-dose DOAC, $n = 13\,049$), 1163 (1.6%) experienced a first post-randomization ischemic stroke while on study drug and were included in the primary analysis (see Supplementary data online, *Figure S1*). Of those, 438 patients (37.7%) had been randomized to warfarin, 434 (37.3%) to a standard-dose DOAC, and 291 (25.0%) to a lower-dose DOAC regimen (*Table 1*). Overall, the median age at the time of enrollment in the original trials was 73 years, 39.3% were female, and 35.4% had already had a stroke prior to enrollment in the RE-LY, AVERROES, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48 trials. The median (25–75th percentile) CHA_2DS_2-VASc score at the time of trial enrollment was 4 (3–6). Baseline characteristics of patients not experiencing an ischemic stroke are shown in Supplementary data online, *Table S2*.

Recurrent ischemic stroke

During a median (interquartile range) continued follow-up of 337 (102–617) days following a first post-randomization ischemic stroke, 74 patients (6.4%) had a recurrent ischemic stroke (*Figure 1*). The risk of recurrent ischemic stroke was particularly high in the first months following the index event, with a cumulative incidence of 3.0% (95% CI 1.9%–4.0%) at 3 months. The cumulative incidence of recurrent ischemic stroke was 7.0% (95% CI 5.2%–8.7%) at 1 year and 10.3% (95% CI 7.8%–12.8%) at 2 years.

An analysis in the original study population of 1163 patients that accounted for the competing risk of death yielded results that

were consistent with the primary analysis, with a cumulative incidence of recurrent ischemic stroke of 6.2% (95% CI 4.8%–7.9%) at 1 year.

Overall, a total of 476 patients (40.9%) permanently discontinued study drug up until day 14 following the first post-randomization ischemic stroke. The corresponding rates according to treatment were 36.5% of patients randomized to warfarin and 48.8% and 35.7% of those randomized to receive a standard-dose and lower-dose DOAC regimen, respectively (see Supplementary data online, *Table S3*). Detailed information on antithrombotic therapy following permanent discontinuation of study drug was not available in the dataset. Hence, a second sensitivity analysis, excluding the first 2 weeks after the first post-randomization ischemic stroke, only including patients alive, at risk and without permanent discontinuation through day 14 was performed ($n = 640$). This analysis too yielded an estimate for the risk of recurrent ischemic stroke that was consistent with the primary analysis, with a cumulative incidence of 6.8% (95% CI 4.6%–8.9%) at 1 year (see Supplementary data online, *Figure S2*).

Table 1 Baseline characteristics (at the time of trial enrollment)

	All ($n = 1163$)	Warfarin ($n = 438$)	Standard-dose DOAC[a] ($n = 434$)	Lower-dose DOAC[b] ($n = 291$)
Age (years), median (IQR)	73 (67–78)	74 (68–79)	72 (66–77)	73 (67–78)
Female sex, *n* (%)	457 (39.3)	172 (39.3)	174 (40.1)	111 (38.1)
Heart failure, *n* (%)	542 (46.6)	200 (45.7)	209 (48.2)	133 (45.7)
Hypertension, *n* (%)	1008 (86.7)	379 (86.5)	380 (87.6)	249 (85.6)
Diabetes mellitus, *n* (%)	375 (32.2)	143 (32.7)	142 (32.7)	90 (30.9)
Coronary artery disease, *n* (%)	363 (31.9) [25]	132 (30.1)	136 (33.3) [25]	95 (32.7)
Prior myocardial infarction, *n* (%)	187 (16.4) [25]	78 (17.8)	61 (14.9) [25]	48 (16.5)
History of any stroke (prior to study entry), *n* (%)	412 (35.4)	163 (37.2)	154 (35.5)	95 (32.7)
History of TIA (prior to study entry), *n* (%)	183 (15.7)	73 (16.7)	76 (17.5)	34 (11.7)
History of any stroke and/or TIA (prior to study entry), *n* (%)	539 (46.3)	215 (49.1)	203 (46.8)	121 (41.6)
Creatinine clearance (mL/min), median (IQR)[c]	63.9 (50.5–84.3) [2]	62.0 (50.3–80.0) [1]	65.0 (50.0–87.5) [1]	63.0 (50.7–86.0)
Smoking [2]				
Current, *n* (%)	102 (8.8)	39 (8.9)	37 (8.6)	26 (8.9)
Former, *n* (%)	390 (33.6)	138 (31.5)	153 (35.4)	99 (34.0)
Never, *n* (%)	669 (57.6)	261 (59.6)	242 (56.0)	166 (57.0)
Body weight (kg), median (IQR)	77.1 (67.0–90.0) [1]	76.0 (66.1–89.9) [1]	78.0 (67.0–90.3)	78 (67.0–91.0)
Body mass index (kg/m^2), median (IQR)	27.7 (24.5–31.3) [3]	27.3 (24.5–30.9) [2]	27.9 (24.6–31.4) [1]	27.9 (24.7–31.9)
Race/ethnicity				
Asian, *n* (%)	249 (21.4)	101 (23.1)	88 (20.3)	60 (20.6)
Black, *n* (%)	11 (0.9)	6 (1.4)	3 (0.7)	2 (0.7)
White, *n* (%)	849 (73.0)	308 (70.3)	327 (75.3)	214 (73.5)
Other, *n* (%)	54 (4.6)	23 (5.3)	16 (3.7)	15 (5.2)
CHA_2DS_2-VASc score				
Median (IQR)	4 (3–6)	5 (4–5)	4 (3–6)	4 (3–6)
0–1, *n* (%)	14 (1.2)	6 (1.4)	4 (0.9)	4 (1.4)
2, *n* (%)	92 (7.9)	21 (4.8)	47 (10.8)	24 (8.2)
3–4, *n* (%)	499 (42.9)	187 (42.7)	177 (40.8)	135 (46.4)
5 or greater, *n* (%)	558 (48.0)	224 (51.1)	206 (47.5)	128 (44.0)

Note: [*n*] denotes the number of patients with missing data.
IQR, interquartile range; DOAC, direct oral anticoagulant; TIA, transient ischemic attack.
[a]Standard-dose DOAC: dabigatran 150 mg twice daily, apixaban 5 mg (2.5 mg if dose reduction criteria were met) twice daily, rivaroxaban 20 mg (15 mg if dose reduction criteria were met) once daily, or edoxaban 60 mg (30 mg if dose reduction criteria were met) once daily.
[b]Lower-dose DOAC: dabigatran 110 mg twice daily or edoxaban 30 mg (15 mg if dose reduction criteria were met) once daily.
[c]Calculated using the Cockcroft–Gault formula.

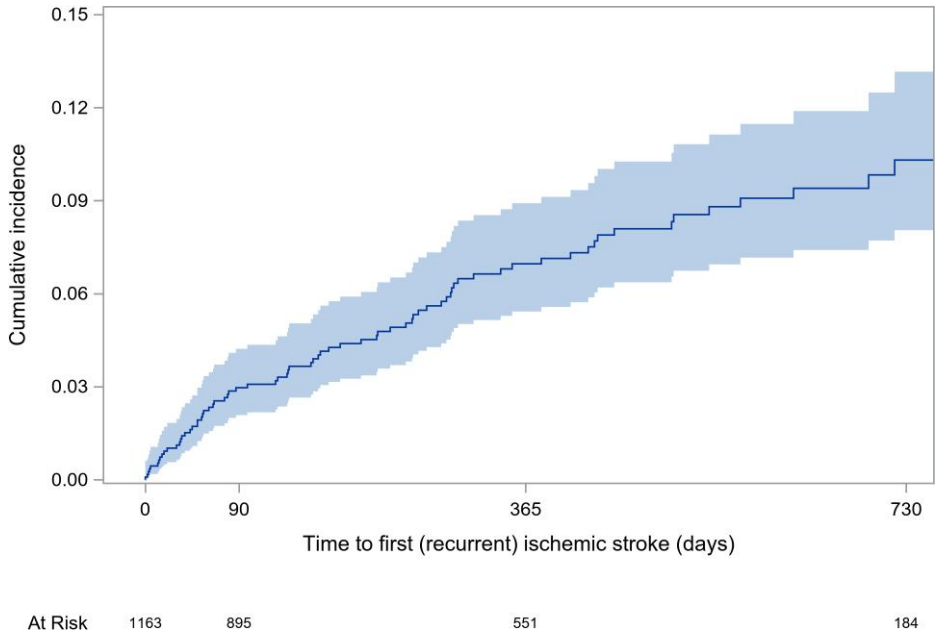


Figure 1 Recurrent ischemic stroke. Figure truncated at 2 years after the first post-randomization ischemic stroke. The shaded area indicates the 95% confidence interval.

A third sensitivity analysis, excluding patients randomized to a lower-dose DOAC regimen [i.e. dabigatran 110 mg twice daily and edoxaban 30 mg once daily (15 mg for patients who met the prespecified criteria)] ($n = 872$), yielded a consistent but slightly reduced estimate for the risk of recurrent ischemic stroke, with a cumulative incidence of 5.5% (95% CI 3.7%–7.2%) at 1 year (see Supplementary data online, *Figure S3*).

Finally, patients with a history of any stroke prior to study entry had a higher risk of recurrent ischemic stroke than patients without a history of stroke prior to study entry (cumulative incidence at 1 year, 10.4% [95% CI 7.4%–14.5%] vs. 5.1% [95% CI 3.5%–7.2%]) (see Supplementary data online, *Figure S4*).

All-cause stroke

In the primary cohort, 85 patients (7.3%) had an all-cause stroke following a first post-randomization ischemic stroke while on oral anticoagulation (see Supplementary data online, *Figure S5*). The cumulative incidence of all-cause stroke was 3.3% (95% CI 2.2%–4.4%) at 3 months and 8.1% (95% CI 6.3%–10.0%) and 11.6% (95% CI 9.0%–14.3%) at 1 and 2 years after the index stroke event, respectively.

Mortality

Of the 1163 patients included in the primary analysis, 235 (20.2%) died during follow-up (*Figure 2*). The majority of deaths (77.4%) were classified as cardiovascular. The risk of death was particularly high in the early time period following the index stroke event, with a cumulative incidence of 12.4% (95% CI 10.5%–14.4%) at 3 months. The cumulative incidence of all-cause mortality was 18.1% (95% CI 15.7%–20.4%) at 1 year and 25.0% (95% CI 21.8%–28.2%) at 2 years after the index event.

Discussion

Using individual participant data from five pivotal randomized trials of antithrombotic therapy in patients with AF, we studied the risk of recurrent ischemic stroke and mortality following a first post-randomization ischemic stroke while on oral anticoagulation. The pooled cumulative incidence of recurrent ischemic stroke in patients with an index stroke while on warfarin, a standard-dose or a lower-dose DOAC regimen, was 7.0% at 1 year. The cumulative incidence of all-cause mortality following the first post-randomization ischemic stroke was 12.4% at 3 months and 18.1% at 1 year (*Structured Graphical Abstract*).

In patients with AF, prior stroke or transient ischemic attack is one of the strongest prognostic factors for future stroke. Hence, prior stroke is a central component of stroke risk scoring systems.[20–22] Subgroup analyses from the RE-LY, AVERROES, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48 trials showed that the relative risk of ischemic stroke during trial follow-up was approximately doubled in patients with a history of stroke or transient ischemic attack prior to study entry (range 1.8–2.9 vs. 0.7–1.4 per 100 patient-years).[3–7] In these analyses, the status of oral anticoagulation use at the time of stroke prior to enrollment was not considered or was unknown, and patients with very recent (i.e. within 7–30 days) or, in two of the trials, severe stroke within 3–6 months prior to enrollment were excluded. Our results suggest that the rate of stroke recurrence despite oral anticoagulation is particularly high in patients treated with oral anticoagulation at the time of the index event. Furthermore, the risk of recurrent ischemic stroke seems to be non-linear and especially high in the first year, corroborating findings from observational cohort studies.[23–25] In the individual trials of DOAC therapy in AF, lower-dose DOAC regimens were non-inferior to warfarin in reducing all-cause stroke or systemic embolism, partly driven by a significant reduction in hemorrhagic stroke. However,

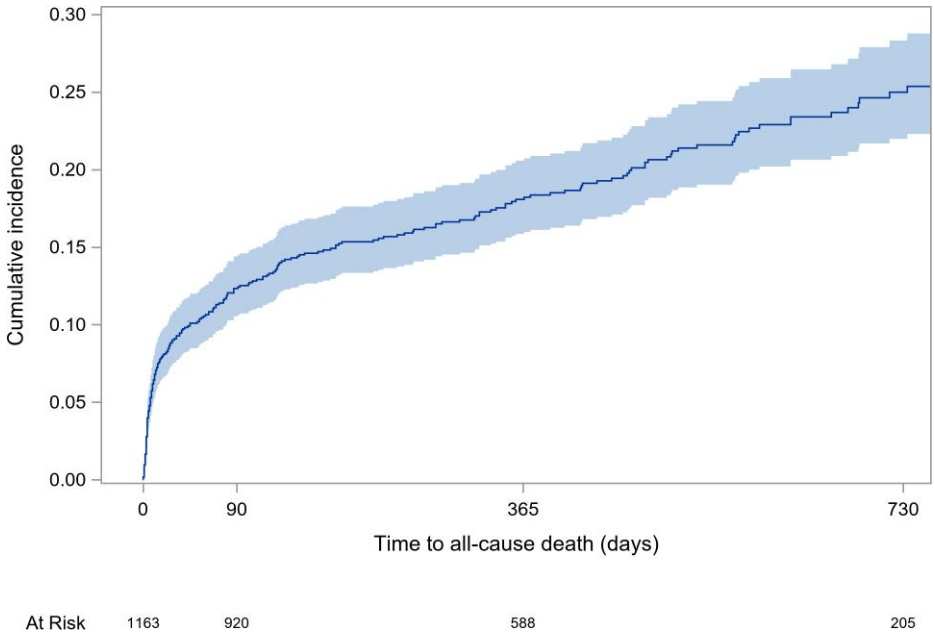


Figure 2 All-cause mortality. Figure truncated at 2 years after the first post-randomization ischemic stroke. The shaded area indicates the 95% confidence interval.

compared with warfarin, there was a numerical increase in ischemic or unspecified stroke with dabigatran 110 mg twice daily (a 27% decrease in dose from the 150 mg regimen) in RE-LY (relative risk 1.11, 95% CI 0.89–1.40, $P = 0.35$) and a statistically significant 41% relative increase in ischemic stroke with the lower-dose edoxaban regimen of 30/15 mg once daily (a 50% decrease in dose from the 60/30 mg regimen) in ENGAGE AF-TIMI 48 [hazard ratio 1.41, 95% CI 1.19–1.67, $P < 0.001$].[8,12] Accordingly, in our study, the cumulative incidence of recurrent ischemic stroke was 5.5% at 1 year in a sensitivity analysis excluding patients who had been randomized to a lower-dose DOAC regimen.

The high mortality rate of 12.4% at 3 months or 18.1% at 1 year following a first post-randomization ischemic stroke is in line with previous observational studies.[23,26] The steep increase in risk early after an index stroke event suggests that either the stroke itself or stroke-related complications may drive mortality in this high-risk population. The observed post-stroke mortality rate in the first year exceeds the baseline mortality rate of anticoagulated patients observed during the individual trials (2.7–4.9 per 100 patient-years overall and 3.2–5.2 per 100 patient-years in those with a history of stroke).[3,5–12]

At present, there is uncertainty of how best to treat such patients experiencing an ischemic stroke while on oral anticoagulation. First, there are no data from randomized trials that support switching from one oral anticoagulant to another.[27] Second, data on the optimal timing of re-initiation of oral anticoagulation after stroke are scarce, but several trials addressing this question are currently underway or have recently been published.[27,28] Based on expert consensus and data from observational cohort studies, most guidelines suggest that it may be reasonable to re-initiate anticoagulation within 2 weeks from stroke onset.[29,30] Others state that a recommendation on the optimal timing of re-initiation cannot be made until randomized trials are completed.[31] Of note, the addition of an antiplatelet agent to oral anticoagulation with rivaroxaban in a Japanese population of patients with AF and stable coronary artery disease was stopped early due to excess mortality in the dual antithrombotic therapy group.[32] While not confined to a secondary prevention population, a meta-analysis of randomized trials in patients with AF found a signal for an increase in both ischemic and all-cause stroke with antiplatelet therapy added on top of oral anticoagulation.[33] The recent LAAOS III trial showed that surgical occlusion of the left atrial appendage in patients with AF undergoing cardiac surgery for another indication reduced a composite of ischemic stroke or systemic embolism by 33%.[34] Importantly, this reduction in stroke was observed in addition to the use of oral anticoagulation. While not directly transferable to percutaneous closure of the left atrial appendage, a combination of a mechanical device with systemic therapy by means of oral anticoagulation may indeed be beneficial for AF patients with an ischemic stroke despite treatment with oral anticoagulation and deserves evaluation in adequately powered, randomized clinical trials.

Finally, although cardioembolism is a frequent mechanism of stroke in patients with AF, other etiologies such as lacunar stroke or stroke due to small vessel disease may not be amenable to antithrombotic therapy alone. Many patients with AF have other risk factors (e.g. hypertension, diabetes mellitus, obesity, or dyslipidemia) that are associated with an increased risk of adverse cardiovascular events, including stroke. Current guidelines for the management of patients with AF highlight the importance of lifestyle intervention and modification of cardiovascular risk factors.[30]

Limitations

This analysis has several limitations. First, the rate of early permanent discontinuation of study drug following a first post-randomization ischemic stroke was high. Second, detailed information on antithrombotic therapy after permanent discontinuation was not available in the

COMBINE AF dataset. However, it is likely that most patients who permanently discontinued study drug were subsequently treated with an open-label oral anticoagulant. Third, with the exception of RE-LY, investigators were blinded as to whether patients were receiving a DOAC or warfarin.[8] The influence of blinding on the rate of study drug discontinuation remains unclear. Fourth, most patients were assumed to at least temporarily discontinue oral anticoagulation following an ischemic stroke, but granular data on temporary discontinuation and the timing of re-initiation of anticoagulation after the first post-randomization ischemic stroke were not available for all trials included in the COMBINE AF dataset. However, a landmark analysis excluding the first 2 weeks after a first post-randomization ischemic stroke, only including those without permanent discontinuation of study drug since the index event yielded a consistent estimate for the incidence of recurrent ischemic stroke. Fifth, the terms 'standard-dose' and 'lower-dose' refer to the DOAC dosing strategies tested in the individually randomized trials, but there is some variation in regulatory approval status and in dosing recommendations of DOACs across current guidelines.[27,29] Sixth, the dataset used for this analysis did not include detailed information on adherence to oral anticoagulation, risk factor control during follow-up (e.g. hypertension or diabetes management), and stroke mechanism or severity. Seventh, the number of outcome events following a first post-randomization ischemic stroke was limited. Finally, this analysis was done in patients enrolled in randomized clinical trials of antithrombotic therapy in AF which may limit its external validity.

Conclusions

Patients with AF who suffer an ischemic stroke while on oral anticoagulation are at increased risk of recurrent ischemic stroke and death. Randomized trials are needed to evaluate strategies aimed at improving outcomes in this population.

Supplementary data

Supplementary data is available at *European Heart Journal* online.

Data availability

Considering pre-existing data privacy restrictions, de-identified data from this study may be made available for other researchers on reasonable request to the COMBINE AF executive committee.

Conflict of interest

A.P.B. has nothing to disclose. S.H.H. reports consulting and lecture fees from Bayer AG, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, and Pfizer. J.W.E. reports institutional research grants and honoraria from AstraZeneca, Bayer AG, Boehringer Ingelheim, Bristol Myers Squibb/Pfizer, Daiichi Sankyo, Eli Lilly and Company, GlaxoSmithKline, Janssen, and Sanofi. A.P.C. has nothing to disclose. R.P.G. reports honoraria for CME programs and lectures from Artivion, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly and Company, Janssen, Pfizer, SAJA Pharmaceuticals, Samsung, and Servier; grants and personal fees from Amgen, Daiichi Sankyo, and Merck; and grants from Anthos Therapeutics outside the submitted work. C.B.G. reports personal fees from Bayer AG and Boston Scientific; grants and personal fees from Boehringer Ingelheim, Bristol Myers Squibb, Janssen, and Pfizer; grants from Daiichi Sankyo during the conduct of the study; personal fees from AbbVie, Espero, Medscape, Medtronic Inc., Merck, the National Institutes of Health, Novo Nordisk, Roche, Rho Pharmaceuticals, CeleCor, Correvio, Philips, Abiomed, and Anthos Therapeutics; grants from Akros, AstraZeneca, the US Food and Drug Administration, GlaxoSmithKline, Medtronic Foundation, and Apple; and grants and personal fees from Novartis and The Medicines Company outside the submitted work. J.H. reports salary support from T32 training grant T32HL069749. Z.H. reports lecture fees from Boehringer Ingelheim, Bristol Myers Squibb, Pfizer, and Roche Diagnostics and consulting fees from Boehringer Ingelheim, Bristol Myers Squibb, Merck Sharp & Dohme, Pfizer, and Roche Diagnostics. He receives research support from the Swedish Society for Medical Research (S17–0133), the Swedish Heart-Lung Foundation (20200722), and Uppsala University Hospital, Sweden.. D.A.M. reports being a member of the Thrombolysis in Myocardial Infarction (TIMI) Study Group, which has received institutional research grant support through Brigham and Women's Hospital from Abbott, Amgen, Anthos Therapeutics, AstraZeneca, Bayer HealthCare Pharmaceuticals Inc., Daiichi Sankyo, Eisai, Intarcia, MedImmune, Merck, Novartis, Pfizer, Quark Pharmaceuticals, Regeneron Pharmaceuticals Inc., Roche, Siemens Healthcare Diagnostics Inc., The Medicines Company, and Zora Biosciences. M.R.P. reports research grants from Bayer AG, Janssen, HeartFlow, and the National Heart, Lung, and Blood Institute (NHBLI) and advisory board/consulting from Bayer AG, Janssen, and Novartis. D.J.S. reports institutional research funding from the Swiss Heart Foundation, the Swiss National Science Foundation, the Bangerter-Rhyner Foundation, and Portola/Alexion Pharmaceuticals. A.S. reports research support from the National Institutes of Health (NIH) [National Institute of Neurological Disorders and Stroke (NINDS) U01NS102289 and National Institute on Aging (NIA) UF1NS120871), Canadian Institutes for Health Research, Heart and Stroke Foundation of Canada, and the Marta and Owen Boris Foundation. He has additionally received research support from Daiichi Sankyo, Bristol Myers Squibb, Bayer AG, and Servier Canada, as well as advisory/speakers bureau honoraria from Daiichi Sankyo, Bayer AG, Takeda Pharmaceutical Company, and Servier Canada. L.W. reports institutional research grants from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb/Pfizer, GlaxoSmithKline, Roche Diagnostics, and Merck & Co and consulting fees from Abbott. He holds two patents involving GDF-15 licensed to Roche Diagnostics (EP2047275B1 and US8951742B2). Q.Y. has nothing to disclose. S.J.C. reports institutional research grants and honoraria from Boehringer Ingelheim, Portola/Alexion Pharmaceuticals, Bristol Myers Squibb/Pfizer, Bayer AG, and Daiichi Sankyo.

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References

1. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;**146**:857–867. https://doi.org/10.7326/0003-4819-146-12-200706190-00007
2. Carnicelli AP, Hong H, Connolly SJ, Eikelboom J, Giugliano RP, Morrow DA, *et al.* Direct oral anticoagulants versus warfarin in patients with atrial fibrillation: patient-level network meta-analyses of randomized clinical trials with interaction testing by age and sex. *Circulation* 2022;**145**:242–255. https://doi.org/10.1161/circulationaha.121.056355
3. Diener HC, Connolly SJ, Ezekowitz MD, Wallentin L, Reilly PA, Yang S, *et al.* Dabigatran compared with warfarin in patients with atrial fibrillation and previous transient ischaemic attack or stroke: a subgroup analysis of the RE-LY trial. *Lancet Neurol* 2010;**9**:1157–1163. https://doi.org/10.1016/s1474-4422(10)70274-x
4. Diener HC, Eikelboom J, Connolly SJ, Joyner CD, Hart RG, Lip GY, *et al.* Apixaban versus aspirin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a predefined subgroup analysis from AVERROES, a randomised trial. *Lancet Neurol* 2012;**11**:225–231. https://doi.org/10.1016/s1474-4422(12)70017-0

5. Easton JD, Lopes RD, Bahit MC, Wojdyla DM, Granger CB, Wallentin L, *et al.* Apixaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of the ARISTOTLE trial. *Lancet Neurol* 2012; **11**:503–511. https://doi.org/10.1016/s1474-4422(12)70092-3
6. Hankey GJ, Patel MR, Stevens SR, Becker RC, Breithardt G, Carolei A, *et al.* Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF. *Lancet Neurol* 2012;**11**: 315–322. https://doi.org/10.1016/s1474-4422(12)70042-x
7. Rost NS, Giugliano RP, Ruff CT, Murphy SA, Crompton AE, Norden AD, *et al.* Outcomes with edoxaban versus warfarin in patients with previous cerebrovascular events: findings from ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48). *Stroke* 2016;**47**:2075–2082. https://doi.org/10.1161/strokeaha.116.013540
8. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–1151. https://doi.org/10.1056/NEJMoa0905561
9. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, *et al.* Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;**364**:806–817. https://doi.org/10.1056/NEJMoa1007432
10. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, *et al.* Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**:883–891. https://doi.org/10.1056/NEJMoa1009638
11. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, *et al.* Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981–992. https://doi.org/10.1056/NEJMoa1107039
12. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, *et al.* Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;**369**: 2093–2104. https://doi.org/10.1056/NEJMoa1310907
13. Carnicelli AP, Hong H, Giugliano RP, Connolly SJ, Eikelboom J, Patel MR, *et al.* Individual patient data from the pivotal randomized controlled trials of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation (COMBINE AF): design and rationale: from the COMBINE AF (A Collaboration Between Multiple Institutions to Better Investigate Non-vitamin K Antagonist Oral Anticoagulant Use in Atrial Fibrillation) investigators. *Am Heart J* 2021;**233**:48–58. https://doi.org/10.1016/j.ahj.2020.12.002
14. Ezekowitz MD, Connolly S, Parekh A, Reilly PA, Varrone J, Wang S, *et al.* Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. *Am Heart J* 2009;**157**:805–810, 810.e801–802. https://doi.org/10.1016/j.ahj.2009.02.005
15. Eikelboom JW, O'Donnell M, Yusuf S, Diaz R, Flaker G, Hart R, *et al.* Rationale and design of AVERROES: apixaban versus acetylsalicylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment. *Am Heart J* 2010;**159**:348–353.e341. https://doi.org/10.1016/j.ahj.2009.08.026
16. Lopes RD, Alexander JH, Al-Khatib SM, Ansell J, Diaz R, Easton JD, *et al.* Apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (ARISTOTLE) trial: design and rationale. *Am Heart J* 2010;**159**:331–339. https://doi.org/10.1016/j.ahj.2009.07.035
17. ROCKET AF Study Investigators. Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation: rationale and design of the ROCKET AF study. *Am Heart J* 2010;**159**: 340–347.e341. https://doi.org/10.1016/j.ahj.2009.11.025
18. Ruff CT, Giugliano RP, Antman EM, Crugnale SE, Bocanegra T, Mercuri M, *et al.* Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: design and rationale for the Effective Anticoagulation with factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction study 48 (ENGAGE AF-TIMI 48). *Am Heart J* 2010;**160**:635–641. https://doi.org/10.1016/j.ahj.2010.06.042
19. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;**94**:496–509. https://doi.org/10.1080/01621459.1999.10474144
20. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;**285**:2864–2870. https://doi.org/10.1001/jama.285.22.2864
21. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. *Chest* 2010;**137**: 263–272. https://doi.org/10.1378/chest.09-1584
22. Hijazi Z, Lindbäck J, Alexander JH, Hanna M, Held C, Hylek EM, *et al.* The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. *Eur Heart J* 2016;**37**:1582–1590. https://doi.org/10.1093/eurheartj/ehw054
23. Seiffge DJ, De Marchis GM, Koga M, Paciaroni M, Wilson D, Cappellari M, *et al.* Ischemic stroke despite oral anticoagulant therapy in patients with atrial fibrillation. *Ann Neurol* 2020;**87**:677–687. https://doi.org/10.1002/ana.25700
24. Polymeris AA, Meinel TR, Oehler H, Hölscher K, Zietz A, Scheitz JF, *et al.* Aetiology, secondary prevention strategies and outcomes of ischaemic stroke despite oral anticoagulant therapy in patients with atrial fibrillation. *J Neurol Neurosurg Psychiatry* 2022; **93**:588–598. https://doi.org/10.1136/jnnp-2021-328391
25. Paciaroni M, Caso V, Agnelli G, Mosconi MG, Giustozzi M, Seiffge DJ, *et al.* Recurrent ischemic stroke and bleeding in patients with atrial fibrillation who suffered an acute stroke while on treatment with nonvitamin K antagonist oral anticoagulants: the RENO-EXTEND study. *Stroke* 2022;**53**:2620–2627. https://doi.org/10.1161/strokeaha.121.038239
26. Meinel TR, Branca M, De Marchis GM, Nedeltchev K, Kahles T, Bonati L, *et al.* Prior anticoagulation in patients with ischemic stroke and atrial fibrillation. *Ann Neurol* 2021;**89**: 42–53. https://doi.org/10.1002/ana.25917
27. Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG, *et al.* 2021 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Europace* 2021;**23**:1612–1676. https://doi.org/10.1093/europace/euab065
28. Oldgren J, Åsberg S, Hijazi Z, Wester P, Bertilsson M, Norrving B. Early versus delayed non-vitamin K antagonist oral anticoagulant therapy after acute ischemic stroke in atrial fibrillation (TIMING): a registry-based randomized controlled noninferiority study. *Circulation* 2022;**146**:1056–1066. https://doi.org/10.1161/circulationaha.122.060666
29. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, *et al.* 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2019;**74**:104–132. https://doi.org/10.1016/j.jacc.2019.01.011
30. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, *et al.* 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;**42**:373–498. https://doi.org/10.1093/eurheartj/ehaa612
31. Klijn CJ, Paciaroni M, Berge E, Korompoki E, Kõrv J, Lal A, *et al.* Antithrombotic treatment for secondary prevention of stroke and other thromboembolic events in patients with stroke or transient ischemic attack and non-valvular atrial fibrillation: a European Stroke Organisation guideline. *Eur Stroke J* 2019;**4**:198–223. https://doi.org/10.1177/2396987319841187
32. Yasuda S, Kaikita K, Akao M, Ako J, Matoba T, Nakamura M, *et al.* Antithrombotic therapy for atrial fibrillation with stable coronary disease. *N Engl J Med* 2019;**381**: 1103–1113. https://doi.org/10.1056/NEJMoa1904143
33. Benz AP, Johansson I, Dewilde WJM, Lopes RD, Mehran R, Sartori S, *et al.* Antiplatelet therapy in patients with atrial fibrillation: a systematic review and meta-analysis of randomized trials. *Eur Heart J Cardiovasc Pharmacother* 2022;**8**:648–659. https://doi.org/10.1093/ehjcvp/pvab044
34. Whitlock RP, Belley-Cote EP, Paparella D, Healey JS, Brady K, Sharma M, *et al.* Left atrial appendage occlusion during cardiac surgery to prevent stroke. *N Engl J Med* 2021;**384**: 2081–2091. https://doi.org/10.1056/NEJMoa2101897